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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,391	08/21/2003	Martin Gleave	UBC.P-035	9734

57381 7590 03/28/2007

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EXAMINER
BOWMAN, AMY HUDSON

ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,391	GLEAVE ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 11 and 14* is/are rejected.

7)☒ Claim(s) *6-10 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 and 14 are pending in the instant application. It is noted that the sequences have been rejoined as a result of the petition decision on 1/26/2007.

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Response to Arguments--Claim Rejections - 35 USC § 112

Claims 1 stands rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the office actions mailed on 4/14/2006 and 9/18/06, as well as the advisory action mailed on 12/20/06 and reiterated below.

One of ordinary skill in the art would not recognize that applicant was in possession of such a large scope of therapeutic agents, as instantly recited. With regards to claim 1, applicant argues that applicants have no control over inhibitors that have not yet been described in the art. However, the test for written description is possession and applicant clearly is not in possession of any therapeutic agent that is effective to reduce the amount of clusterin in melanoma cells by disclosing antisense oligonucleotides and RNAi inhibitors. The claim embraces a multitude of inhibitors such as small molecule inhibitors, antibodies, miRNAs, ribozymes, aptamers, as well as any other inhibitory agent. Applicant argues In re Fuetterer, which was responded to by the examiner in the office action mailed on 9/18/06. The examiner is not requiring for applicant to discover which possible therapeutic agents will function properly in the method, but rather is requiring a description of an adequate number of species of

therapeutic agents to be used by the method that is commensurate with the scope of the instant claim so that one of ordinary skill in the art would recognize that applicant was in possession of the claimed invention.

New Objections/Rejections

Claim Objections

Claims 6-10 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Krieg et al. (WO 99/51259).

The above claims are directed to a method for treatment of melanoma in a mammalian subject comprising administering to the subject a therapeutic agent effective to reduce the amount of clusterin in the melanoma cells, wherein the therapeutic agent is an oligonucleotide.

Krieg et al. teach methods of treating cancer including melanoma by stimulating an antigen specific response against a cancer antigen. Krieg et al. teach methods of treating cancer, more specifically melanoma, comprising introducing a CpG oligonucleotide to a subject in need thereof. Although Krieg et al. are silent as to the ability of the CpG oligonucleotide to reduce the effective amount of clusterin in the melanoma cells, Krieg et al. teach a method of treating melanoma with an oligonucleotide and the method is therefore considered to necessarily reduce the effective amount of clusterin in the melanoma cells, as instantly recited. The instant claims do not recite that the agent or oligonucleotide needs to have any specific relationship with clusterin, but rather be able to reduce the effective amount of clusterin. Since Krieg et al. teach the active step of administering an agent, more specifically an oligonucleotide, to treat melanoma in a subject in need thereof, the oligonucleotide would necessarily be considered to reduce the effective amount of clusterin as a result of treating melanoma, absent evidence to the contrary. Since melanoma is being reduced by the oligonucleotide of Krieg et al., clusterin present in the cells would necessarily be reduced as well.

As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a

manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Therefore, the instant claims are anticipated by Krieg et al.

Claims 1, 2, 11, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Saijo et al. (Oncology Research, Vol. 6, No. 6, 1994, pages 243-249).

The above claims are directed to a method for treatment of melanoma in a mammalian subject comprising administering to the subject a therapeutic agent effective to reduce the amount of clusterin in the melanoma cells, wherein the therapeutic agent is an oligonucleotide, more specifically an antisense oligodeoxynucleotide. The therapeutic agent is an RNA molecule effective to reduce the amount of clusterin in the melanoma cells by an RNAi mechanism.

Saijo et al. teach a method of administering antisense phosphorothioate oligodeoxynucleotides *in vivo* to mice targeted to LOX melanoma cells and resultant inhibition of tumor growth *in vivo*.

The instant specification discloses "The terms RNA, RNA molecule(s), RNA segment(s) and RNA fragment(s) may be used interchangeably to refer to RNA that mediates RNA interference. These terms include double-stranded RNA, single-stranded RNA..." (see last paragraph on page 5). Therefore, the antisense oligonucleotide of Saijo et al. meets the instant limitation of an RNA molecule that would act via an RNAi mechanism.

Although Saijo et al. are silent as to the ability of the antisense oligonucleotide to reduce the effective amount of clusterin in the melanoma cells, Saijo et al. teach a method of treating cancer with an oligonucleotide targeted to melanoma cells and the method is therefore considered to necessarily reduce the effective amount of clusterin in the melanoma cells, as instantly recited. The instant claims do not recite that the agent or oligonucleotide needs to have any specific relationship with clusterin, but rather be able to reduce the effective amount of clusterin. Since Saijo et al. teach the active step of administering an agent, more specifically an antisense oligonucleotide, to treat cancer via targeting melanoma cells in a subject in need thereof, the oligonucleotide would necessarily be considered to reduce the effective amount of clusterin as a result of treating melanoma, absent evidence to the contrary. Since melanoma cells are being reduced by the oligonucleotide of Saijo et al., clusterin present in the cells would necessarily be reduced as well.

As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 370 F.2d 576, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 312 F.2d 937, 939, 136 USPQ 458, 459 (CCPA 1963). Therefore, the instant claims are anticipated by Saijo et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saijo et al. (Oncology Research, Vol. 6, No. 6, 1994, pages 243-249), as explained in the rejection under 35 U.S.C. 102(b) above, in view of Bennett et al. (US 6,111,094)

The above claims are directed to a method for treatment of melanoma in a mammalian subject comprising administering to the subject a therapeutic agent effective to reduce the amount of clusterin in the melanoma cells, wherein the therapeutic agent is an oligonucleotide, more specifically an antisense oligodeoxynucleotide. The antisense oligonucleotide spans either the translation initiation site or the termination site and is enhanced for in vivo stability with a 2'-O-methoxyethyl modification. The therapeutic agent is an RNA molecule effective to reduce the amount of clusterin in the melanoma cells by an RNAi mechanism.

Saijo et al. teach a method of administering antisense phosphorothioate oligodeoxynucleotides *in vivo* to mice targeted to LOX melanoma cells and resultant inhibition of tumor growth *in vivo*.

The instant specification discloses "The terms RNA, RNA molecule(s), RNA segment(s) and RNA fragment(s) may be used interchangeably to refer to RNA that mediates RNA interference. These terms include double-stranded RNA, single-stranded RNA..." (see last paragraph on page 5). Therefore, the antisense oligonucleotide of Saijo et al. meets the instant limitation of an RNA molecule that would act via an RNAi mechanism.

Although Saijo et al. are silent as to the ability of the antisense oligonucleotide to reduce the effective amount of clusterin in the melanoma cells, Saijo et al. teach a method of treating cancer with an oligonucleotide targeted to melanoma cells and the method is therefore considered to necessarily reduce the effective amount of clusterin in the melanoma cells, as instantly recited. The instant claims do not recite that the agent or oligonucleotide needs to have any specific relationship with clusterin, but rather be able to reduce the effective amount of clusterin. Since Saijo et al. teach the active step of administering an agent, more specifically an antisense oligonucleotide, to treat cancer via targeting melanoma cells in a subject in need thereof, the oligonucleotide would necessarily be considered to reduce the effective amount of clusterin as a result of treating melanoma, absent evidence to the contrary. Since melanoma cells are being reduced by the oligonucleotide of Saijo et al., clusterin present in the cells would necessarily be reduced as well.

Saijo et. al. do not teach antisense oligonucleotides that span either the translation initiation site or the termination site or 2'-O-methoxyethyl modifications.

Bennett et al. teach general antisense oligonucleotide design and teach that

preferable target regions include the start codons of a desired target. Bennett et al. teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl and that such modifications enhance the affinity of the antisense oligonucleotide for a nucleic acid target and increase stability of the oligonucleotide in the presence of nucleases.

It is noted that instant claim 3 does not require for the antisense oligonucleotide to span the translation initiation site or termination site of any specific target sequence. Therefore, any antisense oligonucleotide utilized in a mammalian subject to treat melanoma cells targeted to the translation initiation site or termination site of a target that is effective to reduce melanoma would necessarily reduce clusterin, as explained above.

It would have been obvious to one of ordinary skill in the art to target the antisense oligonucleotides of the method of Saijo et al. to the initiation site, as taught by Bennett et al. It would have been obvious to one of ordinary skill in the art to chemically modify the antisense oligonucleotides of the method of Saijo et al. with 2'-O-methoxyethyl modifications, as taught by Bennett et al.

One would have been motivated to target the antisense oligonucleotides of the method of Saijo et al. to the initiation site because Bennett et al. teach that start codons are a preferable target region for antisense inhibition of target gene expression. One would have been motivated to chemically modify the antisense oligonucleotides of the method of Saijo et al. with 2'-O-methoxyethyl modifications because Bennett et al. teach that 2'-O-methoxyethyl modifications enhance the affinity of antisense oligonucleotides

for a nucleic acid target and increase stability of the oligonucleotide in the presence of nucleases. Furthermore, Saijo et al. teach phosphorothioate modifications have been widely used because of their increased stability to nucleases. It would have been obvious to incorporate another chemical modification, 2'-O-methoxyethyl, which was known to add the same benefits.

Finally, one would have a reasonable expectation of success given that Bennett et al. teaches that start codons are preferable target regions for antisense oligonucleotides. One would reasonably expect for such design to benefit the activity of the oligonucleotide of the method of Saijo et al. as well. Furthermore, one would have a reasonable expectation of success that a 2'-O-methoxyethyl modification would enhance the activity of the oligonucleotides of the method of Saijo et al. because both Saijo et al. and Bennett et al. teach chemical modifications that enhance oligonucleotide stability.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

Amy H Bowman
Examiner
Art Unit 1635

AHB